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ORIGINAL ARTICLE

Distal embolic protection during percutaneous coronary intervention in patients with acute coronary syndromes: The RUBY* study

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Abstract

Objective: To assess the safety and feasibility of the GuardWire^{TM} system as an embolic protection device during percutaneous coronary intervention (PCI) in acute coronary syndromes (ACS). **Background:** Distal embolization occurs in approximately 15% of patients after primary angioplasty and is associated with reduced myocardial reperfusion, more extensive myocardial damage and a poor prognosis. Distal embolic protection could reduce the rate of embolic complications and improve outcome. **Methods:** 329 patients (mean age 60 ± 12 years) were included: 278 (84.5%) with ST-elevation myocardial infarction (STEMI), 50 (15.2%) with unstable angina/non-STEMI and 1 (0.3%) with post-infarction angina. Primary endpoint was the incidence of major adverse cardiac events (MACE) at 30 days. Secondary endpoints were the magnitude of ST-segment resolution at 90 and 180 min post-procedure, myocardial blush grade, and angiographically visible distal emboli. **Results:** The GuardWire^{TM} system was successfully positioned in 99% of patients. Complete ST-elevation resolution ($>70\%$) was observed in 28.5% immediately post-procedure, and in 35.4% and 41.6% at 90 and 180 min post-procedure. TIMI-3 flow grade was achieved by 89.8% of patients after intervention and mean corrected TIMI frame count was 20.2 ± 13.2. Grade-3 myocardial blush was seen in 47.7% of patients and distal emboli were angiographically visible in 7.4%. Incidence of MACE at 30 days was 3.3% (death 1.2%; Q-wave MI 0.3%; non-Q-wave MI 0.3%; coronary artery bypass graft 0.6%; repeat PCI 0.9%). **Conclusion:** The GuardWire^{TM} system was successfully positioned in nearly all patients without complications. The use of this embolic protection device in ACS patients undergoing PCI was associated with low rates of distal embolization and 30-day MACE.

Key Words: *Myocardial infarction, angioplasty, distal protection*

Introduction

Treatment of acute myocardial infarction (AMI) focuses on prompt restoration of epicardial coronary flow through either thrombolytic therapy or percutaneous coronary intervention (PCI). A number of randomized clinical studies have shown that PCI is superior to thrombolytic therapy in the treatment of AMI in terms of restoration of normal coronary blood flow (1–3). PCI is associated with lower rates of recurrent ischemia, stroke, reinfarction, and death. The use of stents in PCI has been shown to provide further improvements in patient outcomes, including post-intervention minimal lumen diameter, restenosis rate, and the occurrence of ischemia, stroke, reinfarction, and death (3,4).

However, recovery of a normal epicardial coronary artery flow does not always lead to the anticipated improvement in myocardial perfusion. In patients where adequate myocardial reperfusion is not achieved, poor functional recovery is generally observed (5). The failure to achieve adequate reperfusion may result from necrosis of the myocytes and microvascular network arising because of either ischemia or the embolization of plaque or thrombus material from the target lesion (6–8).

Distal embolization has been shown to occur in approximately 15% of patients after primary PCI (9), and has been associated with reduced myocardial reperfusion, more extensive myocardial damage and a poor prognosis (7,8). The use of a distal protection device could reduce the complication rate of percutaneous interventions by allowing collection and removal of embolic debris. Two types of distal protection devices are currently in use: distal

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occlusion balloons, which occlude the artery and allow aspiration of debris via a catheter; and distal filters, which trap debris during intervention and are then collapsed and withdrawn (10). The utility of distal embolic protection devices has been demonstrated in a number of studies (11–18).

We present here the results of the RUBY (Revascularization Utilizing Balloon Protection in Acute Coronary Ischemic Syndromes) study. The study was designed to evaluate further the feasibility and safety of the GuardWire^{TM} system as an adjunctive embolic protection device during PCI in patients with acute coronary syndromes (ACS).

Methods

Patients

Patients over 18 years of age with ACS amenable to percutaneous revascularization were eligible for entry into the RUBY study. Inclusion criteria included ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) or unstable angina pectoris (Braunwald class IIIB or IIIC) accompanied by either ischemic ECG changes at rest (ST-segment elevation or depression, left bundle branch block, or T-wave inversion) or a positive troponin test. The onset of symptoms had to be no more than 24 h prior to angiography. An angiogram was performed to confirm that the patient met the angiographic inclusion criteria: a target lesion that was suitable for PCI/stent, located in the proximal or mid-segment of a native vessel, with a visually estimated stenosis of $>50\%$; the target vessel diameter at the lesion site was either known or expected to be between 2.5 and 5.0 mm.

Patients were excluded if they had unprotected left main stenosis ($>50\%$), multivessel coronary artery disease requiring coronary artery bypass surgery instead of or after PCI, excessive vessel tortuosity, diffuse disease or calcification, which may have impeded the passage of the GuardWire^{TM} or Export^{TM} catheter. Other exclusion criteria included major surgery within the preceding six weeks, pregnancy, active significant bleeding, other diseases that may cause non-compliance, limited life expectancy, and known allergy or contraindications to heparin, aspirin, clopidogrel, or ticlopidine.

Study design

RUBY was a prospective, non-randomized, multicenter study. Baseline measurements included demographics, cardiac history, angina status, ECG, and TIMI-flow grade. TIMI flow and myocardial blush assessments, as well as an ECG, were performed immediately post-procedure. Further ECGs were performed at 90 and 180 min post-procedure and at discharge. Ischemia and angina status were assessed at discharge. An independent core laboratory (Diagram BV, Zwolle, The Netherlands) was responsible for the analysis of TIMI flow grade, corrected TIMI frame count, myocardial blush grade and presence of angiographically visible distal emboli. The same core laboratory also classified ST-segment resolution ($<30\%$ no resolution, 30–70% partial resolution, $>70\%$ complete resolution).

Data on the incidence of adverse events, including major adverse cardiac events (MACE) were obtained during the procedure, immediately post-procedure, at 90 and 180 min post-procedure, at discharge, and at 30-day follow-up. MACE included death, Q-wave and non-Q-wave MI, emergent bypass surgery, and target lesion revascularization (coronary artery bypass graft or repeat PCI).

Endpoints

The primary endpoint was the incidence of MACE at 30 days. Secondary endpoints were the magnitude of ST-segment resolution at 90 and 180 min post-procedure, myocardial blush grade, and angiographically visible distal emboli.

GuardWire^{TM} system

The GuardWire^{TM} temporary occlusion and aspiration system (Medtronic, Inc. Minneapolis, MN) has been described elsewhere (14). In brief, it comprises:

(a) a 0.014" guidewire with a distally incorporated occlusion balloon whose size range may accommodate vessel diameters between 2.0 and 5.0 mm;
(b) an aspiration catheter (Export^{TM}; Medtronic, Inc. Minneapolis, MN) that can be advanced over the GuardWire^{TM} to remove embolic debris, and can also be used to locally infuse diagnostic or therapeutic agents into the target vessel; and
(c) an inflation and deflation device (MicroSeal^{TM} adapter with EZ Flator^{TM}; Medtronic, Inc. Minneapolis, MN) (Figure 1).

Angioplasty procedure

The primary goals of the procedure were to perform PCI/stent of the target lesion according to routine hospital practice, and to remove as much debris as possible while maintaining maximum distal protection by keeping the GuardWire^{TM} balloon inflated during all phases of the interventional procedures. The initial attempt to cross the lesion was made with the GuardWire^{TM}. If the crossing of the lesion was completed successfully, the device was placed

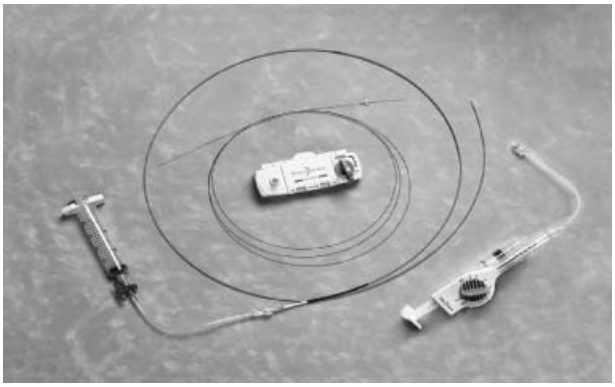


Figure 1. The GuardWire™ device.

30–35 mm distal to the target lesion in the dominant branch of the infarct-related artery.

If the GuardWire™ could not be positioned correctly, a conventional coronary guidewire was used as a 'buddy wire' to facilitate advancement and lesion crossing of the device. If this failed, aspiration was performed using the Export™ catheter over the standard guidewire, followed by a second attempt to position the GuardWire™ device. If this second attempt was unsuccessful, predilatation with a 1.5-mm PCI balloon followed by aspiration with the Export™ catheter could be used prior to a further attempt to introduce the GuardWire™. However, a subsequent failure to correctly position the device was recorded as 'failure to cross', and the procedure was performed without distal protection.

Correct position of the occlusion balloon was assessed angiographically to ensure safe inflation and distal occlusion. If the position of the occlusion balloon could not be verified, the balloon was not inflated, and an aspiration followed by repeat angiography was performed. In cases of continued non-visualization, nitroglycerin (NTG) was administered (unless contraindicated due to hypotension) and if necessary predilatation with a 1.5-mm PCI balloon followed by aspiration was performed. The procedure was completed without distal protection if the distal vessel could not be visualized.

Following vessel occlusion by the GuardWire™ balloon inflation, angioplasty or stenting (direct or with predilatation) was performed at the discretion of the investigator. Following the final stent expansion, a minimum of two-syringe aspirations were performed. If debris were recovered at the second aspiration, additional syringe aspirations were performed until no further debris was extracted. The GuardWire™ balloon was then deflated and removed. Intra-coronary NTG (100–200 μg) was administered before performing the final angiography.

Concomitant medications, including aspirin, heparin, glycoprotein IIb/IIIa inhibitors, clopidogrel, or ticlopidine were administered pre- and post-procedure according to hospital routine. Aspirin was administered to all patients at a dose ranging between 100 and 325 mg per day, and clopidogrel (75 mg per day) or ticlopidine (250 mg twice daily) in case of stent implantation.

Follow-up procedure

Clinical follow-up was performed at 30 ± 5 days post-procedure. The visit could be performed either by the referring cardiologist or, alternatively, via telephone contact. Clinical assessments at follow-up included evaluation of ischemia and angina status, adverse events and MACE.

Statistical analysis

All data were analyzed on an intent-to-treat basis. The statistical analysis was based on descriptive statistical techniques, including 95% confidence intervals. A sample size of 250 was selected, but this was not intended to provide statistical hypothesis testing for this device. Subgroup analysis was performed on the study population with respect to the diagnosis of STEMI or NSTEMI and the presence of an occluded or an open vessel at study entry, and the timing of the intervention from symptom onset. Subgroup differences were analyzed using the t-test, chi-squared test or F-test at a level of $\alpha = 0.05$.

Ethics

The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the ethical committee of each study center, as required by local regulations. All patients provided written, informed consent prior to entry into the study.

Results

Patients

Three hundred and twenty-nine patients from 22 centers in Europe, Israel and the Asia-Pacific region were enrolled into the RUBY study. The mean age of the patients was 60 ± 12 years, and 79% were male. The majority of patients (84.5%) were diagnosed with STEMI, while 5.5% were diagnosed with NSTEMI, and 9.7% with unstable angina (UA). One patient (0.3%) was diagnosed with post-infarction UA. Baseline patient and coronary lesion characteristics are shown in Table I.

Overall safety and efficacy

The GuardWire™ system was successfully positioned in 99% of patients, and was successfully inflated in 91.4% of them pre-procedure and in 96.6% during the procedure. Emboli were retrieved

Table I. Baseline characteristics of patients and coronary lesions.

Patient characteristics	
Mean age (years ± SD)	60 ± 12.15
Males % (n/N)	79 (260/329)
Smoking (ex or current) % (n/N)	66 (218/329)
Diabetes (insulin dependent/non-insulin dependent) % (n/N)	17 (56/329)
Hypertension % (n/N)	46.5 (153/329)
Hypercholesterolemia % (n/N)	43 (138/321)
Family history of cardiovascular disease % (n/N)	30 (98/328)
Previous Q-wave MI % (n/N)	10.6 (35/329)
Previous non-Q-wave MI % (n/N)	3.7 (12/326)
Previous CABG % (n/N)	1.2 (4/326)
Previous PCI % (n/N)	9.5 (31/328)
Lesion characteristics	
Mean length (mm SD)	15.9 ± 7.5
Mean reference vessel diameter (mm ± SD)	3.32 ± 0.48
Pre-procedure mean percentage stenosis (% ± SD)	96.7 ± 10.3
Post-procedure mean percentage stenosis (% ± SD)	5.07 ± 11.8

during aspiration in 91.7% of patients pre-procedure, and in 73.4% during the procedure. Most of the patients (86.3%) were treated with direct stenting, 7.9% with stenting after predilation, while 4.3% with balloon dilatation only.

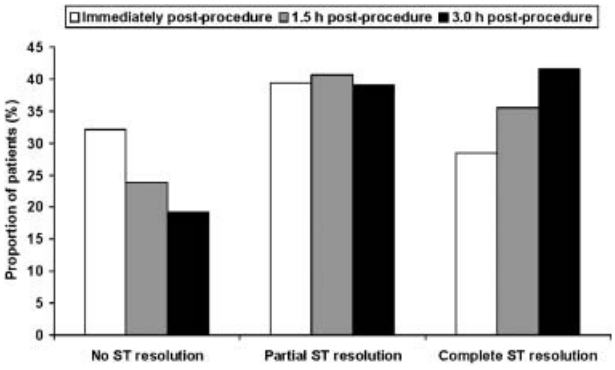


Figure 2. Resolution of ST-segment elevation after PCI (all patients).

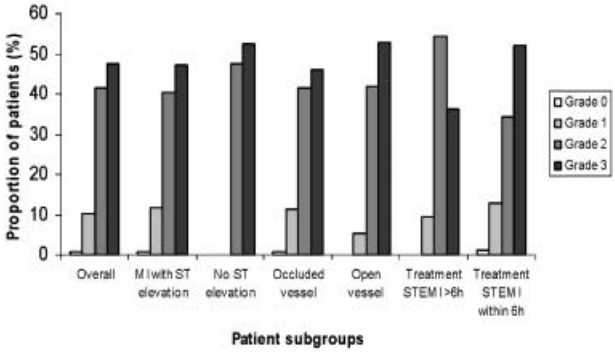


Figure 4. Myocardial blush grade after PCI (overall and for subgroups). STEMI, ST-elevation myocardial infarction.

Of those patient presenting with ST-segment elevation at study entry, 28.5% showed complete ST-segment resolution immediately post-procedure, and 41.6% three hours post-procedure (Figure 2). TIMI-3 flow grade was achieved in 89.8% of patients after intervention (Figure 3), whereas the mean corrected TIMI frame count was 20.2 ± 13.2. Normal myocardial blush (grade 3) was seen in 47.7% of patients (Figure 4). At final angiography evaluation, distal emboli were visible in 7.4%. The incidence of MACE at 30 days was 3.3% (death 1.2%; Q-wave MI 0.3%; non-Q-wave MI 0.3%; CABG 0.6%; repeat PCI 0.9%) (Table II).

Subgroup analysis

Subgroup analysis was performed to assess the effect of ST-segment elevation, vessel occlusion at study entry, and timing of treatment in STEMI patients on clinical outcome.

In patients diagnosed with NSTEMI, there was a slight trend towards greater improvements in myocardial blush scores, with 100% of patients achieving either a grade 2 (47.7%) or 3 score (52.3%) compared with 87.5% (grade 2, 40.5%; grade 3, 47.0%) in STEMI patients (Figure 4). More

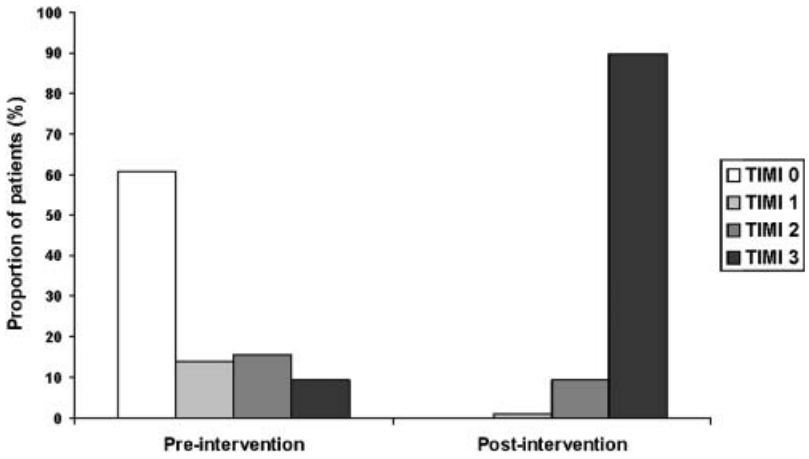


Figure 3. TIMI flow before and after PCI (all patients).

Table II. MACE and other adverse events post-procedure.

	Study Subgroups % (n)						
	STEMI (n=278)	UA/ NSTEMI (n=51)	Occluded vessel (n=249)	Open vessel (n=80)	Intervention > 6 h in STEMI (n=88)	Intervention ⩽ 6 h in STEMI (n=190)	Overall (n=329)
Death (%)	3 (1.1)	1 (2)	4 (1.6)	0	2 (2.3)	1 (0.5)	4 (1.2)
Q-wave MI (%)	1 (0.4)	0	1 (0.4)	0	0	1 (0.5)	1 (0.3)
Non-Q-wave MI (%)	0	1 (2)	1 (0.4)	0	0	0	1 (0.3)
CABG (%)	2 (0.7)	0	1 (0.4)	1 (1.25)	0	2 (1.1)	2 (0.6)
Target lesion re-PCI (%)	3 (1.1)	0	2 (0.8)	1 (1.25)	1 (1.1)	2 (1.1)	3 (0.9)
Total (%)	9 (3.2)	2 (4)	9 (3.6)	2 (2.5)	3 (3.4)	6 (3.2)	11 (3.3)

STEMI, ST-elevation myocardial infarction; UA, unstable angina; NSTEMI, non-ST-elevation myocardial infarction; CABG, coronary artery bypass grafting; PCI: percutaneous coronary intervention.

patients diagnosed with STEMI had a pre-procedural TIMI-flow grade of 0 compared to those diagnosed with NSTEMI (66.6% versus 31.4%); however, the majority of patients in both subgroups achieved a normal TIMI-3 flow grade (88.6% versus 96.1%) after PCI. ST-segment resolution could not be compared between the two groups because most of NSTEMI patients did not have ST-segment elevation at study entry. In patients with STEMI, complete ST-segment resolution at three hours post-procedure was observed in 43.5%. The incidence of MACE was similar in the two groups (Table II).

At study entry, 76% of patients presented with an occluded vessel. The presence of an occluded vessel had no significant effect on any of the outcome measures. More patients with an occluded vessel had complete ST-segment resolution (44.3% versus 30.8%) at 3 hours post-procedure, although the difference was not significant (P=0.26). There were no significant differences in myocardial blush grade improvement between patients with an occluded vessel (41.5% grade 2; 46.1% grade 3) and those with an open vessel (41.9% grade 2; 52.7% grade 3) (Figure 4). Approximately, 90% of patients in both groups achieved TIMI-3 flow grade post-procedure. The overall incidence of MACE was similar in the two groups (Table II); all four deaths, however, occurred in the group of patients with an occluded vessel.

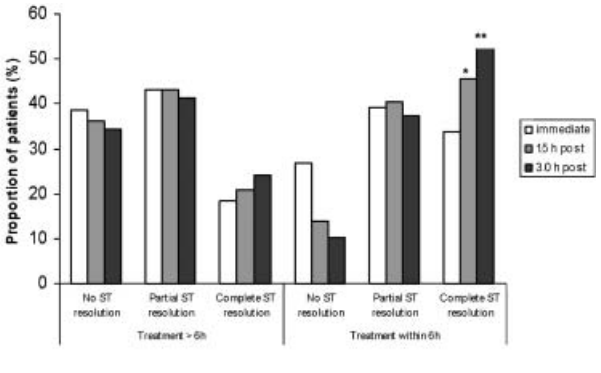
The majority of STEMI patients (68%) received intervention ⩽ 6 hours of symptom onset. Compared to patients treated > 6 hours of symptom onset, they had a significantly higher rate of complete ST segment resolution at 1.5 and 3 h post-procedure (45.5% versus 20.7%, P<0.0001; and 52.4% versus 24.1%, P<0.0001) (Figure 5). Although a similar proportion of patients in both subgroups achieved either a grade 2 or 3 myocardial blush (90.4% in > 6 h treatment group versus 86.2% ⩽ 6 hours treatment group), more patients in the group receiving treatment ⩽ 6 hours achieved a grade 3 myocardial blush post-procedure (51.9% versus 36.2%) (Figure 4). There were no significant differences in the proportion of patients achieving TIMI-3 flow grade post-procedure (89.7% in > 6 h treatment group versus 88.1% in ⩽ 6 h treatment group) and the incidence of MACE between the two groups (Table II).

Discussion

The RUBY study was designed to evaluate the feasibility and safety of using a temporary occlusion and aspiration distal protection device, the GuardWire^{TM} system, to prevent distal embolization in patients with ACS undergoing PCI. Distal embolization can lead to post-procedural complications, notably reduced myocardial perfusion, which can result in a poor prognosis (6–8).

The GuardWire^{TM} system successfully prevented distal embolization, as evidenced by the fact that, at final angiography, visible emboli were detected in 7.4% of patients only. Debris was retrieved in the majority of patients both before PCI (92%) and after stent deployment (73%). TIMI-3 flow grade was observed in almost 90% of patients, consistent with the results from previous primary PCI studies (2,3).

However, TIMI-flow grade describes epicardial rather than myocardial blood flow. Therefore, while restoration of a normal TIMI flow grade may be observed in most patients, many may not achieve normal myocardial perfusion (19). It has been



*P <0.0001 versus treatment >6 h; **P <0.0001 versus treatment >6 h

Figure 5. Effect of treatment timing on ST resolution in ST-segment elevation myocardial infarction patients.

suggested that the success of reperfusion therapy, therefore, should not only be based on the presence of an open infarct-related artery with normal epicardial flow, but also on the evidence of adequate myocardial perfusion (19). Myocardial blush, a measure of the flow through the myocardial capillary bed subtended by the infarcted artery, has been shown to be a more robust measure of long-term outcome following angioplasty, and it is associated with improved left ventricular function and better long-term clinical outcome (20).

Almost half (47.7%) of the patients in the RUBY study achieved grade 3 myocardial blush (normal), and a further 41.6% achieved grade 2 (moderate). Previous studies, where myocardial blush grade has been assessed and longer-term follow-up has been performed, have demonstrated that normalized myocardial perfusion after successful primary PCI is associated with improved long-term outcome (21–23).

The primary endpoint of this study was safety, and the results demonstrate that the use of a distal protection device such as the GuardWire^{TM} system is safe, with a 30-day MACE rate of only 3.3%. The low 30-day incidence of MACE observed in this study compare favorably to the results of previous studies in patients treated with primary PCI (2,4,24).

A subgroup analysis of the RUBY patients showed no significant difference in outcome measures between those with STEMI or NSTEMI, and between those presenting with an occluded or open vessel. In STEMI patients, however, the timing of treatment had a significant effect on both ST-segment resolution and myocardial blush grade. A significantly higher proportion of patients receiving treatment within six hours exhibited ST-segment resolution three hours post-intervention and achieved a normal (grade 3) myocardial blush. The timing of treatment, however, did not affect achievement of TIMI 3 flow. The effect on myocardial blush observed here might suggest that an earlier intervention could contribute to improved longer-term survival, although this would require long-term follow up beyond the scope of this study.

Multicenter studies such as the RUBY offer an opportunity to assess interventions in a more realistic clinical setting compared to clinical trials, where patients must match a highly controlled set of inclusion criteria. The RUBY study shows that distal protection with the GuardWire^{TM} system in patients with ACS is feasible and safe, with a very low incidence of distal embolization and 30-day MACE. These results compare favorably to those seen in previous studies evaluating primary PCI in acute myocardial infarction. Moreover, the results obtained with regard to myocardial blush grade suggest a positive longer-term outcome in these patients. However, further randomized clinical trials will be needed in order to assess fully the safety and effectiveness of the GuardWire^{TM} system.

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Appendix

The RUBY study investigators (with numbers of patients enrolled in parentheses):

AL Bartorelli, F Fabbiocchi, P Montorsi, P Ravagnani, S Galli, G Calligaris, Centro Cardiologico Monzino, Milan, Italy (50); K Tian Hai Koh, National Heart Center, Singapore (50); F Di Pede, Ospedale Civile Umberto I, Mestre, Italy (30); B Reimers, S Saccà, Ospedale Civile di Mirano, Italy (24); L Thuesen, Skejby Hospital, Aarhus, Denmark (23); S Saito, Shonan Kamakura General Hospital, Kamakura, Japan (20); G Hyeon-Cheol, Samsung Medical Center, Seoul, Korea (20); SSL Li, Queen Elisabeth Hospital, Hong Kong, Hong Kong (19); PHMJ Vermeersch, AZ Middelheim, Antwerpen, Belgium (12); S De Servi, Ospedale Civile di Legnano, Legnano, Italy (12); S Beil, Diakonissen Krankenhaus, Augsburg, Germany (11); K Parikh, Sterling Hospital, Ahmedabad, India (10); S Berti, Ospedale G Pasquinucci, Massa, Italy (9); FW Amann, Cardiovascular Center, Zurich, Switzerland (8); H Suryapranata, Isala Klinieken locatie de Weezenlanden, Zwolle, The Netherlands (7); G New, Box Hill, Box Hill, Australia; D Walters, The Prince Charles Hospital, Chermside, Australia (5); M deBelder, James Cook University Hospital, Middlesborough, UK (4); J Weigand, Universitätsklinikum Charité, Berlin, Germany (3); V Legrand, CHU Sart Tilman, Liege, Belgium (2); V Guetta, Sheba Medical Center, Tel Hashomer Ramat-Gan, Israel (2); T Santoso, Medistra, Jakarta, Indonesia (2).